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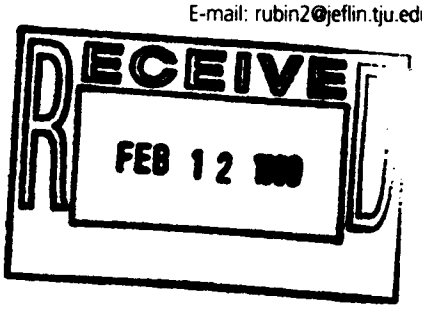


C.W. Jameson, Ph.D.
NTP Report on Carcinogens
MD EC-14
P.O. Box 12233
Reset Triangle Park, NC 27709

RE: Response to Proposed NTP Listing of Alcoholic Beverage Consumption as a Carcinogen

Dear Dr. Jameson:

At its last meeting, December 2-3, 1998, I presented a statement to the NTP on behalf of the beverage alcohol industry in which I commented upon the relationship of alcoholic beverage consumption and the development of cancers of the breast and liver. I indicated that there are substantial questions relating to the validity of studies that claim such a link and that it would be inappropriate to list any alcoholic beverage as a carcinogen at this time. Despite my arguments (and those of Dr. William Waddell), the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee decided to classify alcoholic beverages as a carcinogen. I wish, therefore, to amplify my previous remarks in the hope that this decision will be subjected to careful review.

The question of the carcinogenicity of alcoholic beverages is of more than academic interest. In my opinion, the benefits of moderate alcohol consumption with regard to coronary artery disease, ischemic stroke, and osteoporosis have been well demonstrated. Thus, labeling alcohol as a carcinogen might do considerable mischief by discouraging ordinary social drinking and its protection against serious and common disorders. With respect to alcohol abuse, there are more important reasons to warn the public about its dangers. If we ask whether the consumption of large amounts of alcoholic beverages has carcinogenic effects that are different from those of moderate alcohol consumption, it is appropriate to consider possible confounders associated with alcoholism, which might be responsible for the alleged association. Certainly, intake of excessive amounts of alcohol is not the only difference between alcohol abusers and the general population. In this context many investigators view with skepticism non-experimental studies that demonstrate relative risks less than two, and the New England Journal of Medicine seeks a relative risk of at least three before accepting a paper for publication (1).

**Ethanol as a Putative Carcinogen**

A cursory inspection of the molecular structure of ethanol suggests that it is a poor candidate as a carcinogen. It is a 2-carbon molecule that does not resemble any known carcinogen, e.g. aromatic hydrocarbons, nitrosamines, aflatoxin, etc. Moreover, ethanol is not positive in tests for mutagenicity, including the Ames salmonella assay, sister chromatid exchange, mouse micronucleus assay, and others (2). Experimental animals fed ethanol chronically for a lifetime have not developed malignant tumors, and even subhuman primates fed ethanol as long as 8 to 10 years showed no incidence of cancer. It might be argued that although

ethanol itself is not a carcinogen, it acts as a promoter in the classic initiator/promoter model. However, promoters stimulate cell proliferation, an action that is actually contrary to that of ethanol. Both in tissue culture and in the regenerating liver after partial hepatectomy, it is generally accepted that ethanol inhibits cell proliferation. Thus, ethanol is not a mutagen, initiator or promoter, and on experimental grounds it should not be labeled as a carcinogen.

**Alcoholic Beverages and Cancer of the Liver**

Although the International Agency on Research in Cancer (IARC) has classified alcoholic beverages as a liver carcinogen, this action can be seriously questioned. It is universally recognized that except for the very rare fibrolamellar variant, hepatocellular carcinoma ordinarily arises in the setting of cirrhosis or chronic hepatitis. Since only 10% to 20% of alcoholics develop chronic liver injury (3), some 80-90% of alcoholics are at virtually no risk for hepatocellular carcinoma. With respect to the risk of hepatocellular carcinoma in persons suffering from alcoholic cirrhosis, the studies upon which IARC relied were flawed by poor or absent controls for infection with hepatotropic viruses.

The large majority of cases of hepatocellular carcinoma are associated with hepatitis B or hepatitis C. In this context the prevalence of serum markers for hepatitis B virus (HBV) is 2- to 4-fold higher in alcoholics than in corresponding control populations (4-6). Significantly, 50-80% of alcoholics with cirrhosis who develop hepatocellular carcinoma show serum markers for HBV (6-8), compared to about 25 % in similar patients who are free of cancer. The increased risk for hepatocellular carcinoma among alcoholics infected with HBV is supported by the results of a prospective study of cirrhotic patients, in which the highest incidence of hepatocellular carcinoma was seen in alcoholics who also suffered from hepatitis B (9).

The prevalence of hepatitis C is also much higher in alcoholics than in the general population (10-13). In fact, antibodies against hepatitis C virus (HCV) have been demonstrated in as many as 10% of alcoholics, whereas the prevalence is about 1 % in the general population. Moreover, the highest prevalence (50-70%) of HCV infection among alcoholics has been demonstrated in those with hepatocellular carcinoma (11,13,14).

Owing to the limited sensitivity of tests for HBV and HCV, and the possibility that patterns of viral gene expression and replication may be altered in alcoholics, the frequency of infection with hepatotropic viruses in alcoholics is probably an underestimate of their true distribution. In this respect, in alcoholics with hepatocellular carcinoma whose serum was negative for hepatitis B surface antigen (HbsAg), all demonstrated HBV DNA in the liver, implying a major role for HBV in the pathogenesis of the cancer (6). Thus, the data strongly suggest that most cases of hepatocellular carcinoma in alcoholics should be attributed to chronic viral hepatitis rather than alcoholic beverages and that these beverages are not carcinogenic for the liver.

**Alcoholic Beverages and Breast Cancer**

I have recently reviewed the epidemiological evidence for a causative association between alcohol consumption and the risk of breast cancer. In general the relative risks

described are all small, and they are almost non-existent at moderate levels of alcohol consumption. The risk of confounding in the study of a multifactorial disease such as breast cancer, which involves dietary, hormonal, genetic, socioeconomic and other factors, is substantial, particularly at higher levels of alcohol consumption.

Interest in the possible association of alcohol consumption and breast cancer was initially stimulated by the Third National Cancer Survey (15), in which a weak association between these parameters was reported. Since then a substantial number of epidemiological studies have been published, many confirming the association, but quite a few failing to find any association. To this end, I have recently reviewed 12 cohort studies and almost 50 case-control studies, of which 7 cohort studies and 37 case-control studies supplied sufficient data to look for a dose-response relationship (16).

Some years ago the case for an association between alcohol consumption and breast cancer was reviewed by Steinberg, et al. (17), but Shatzkin, et al. (18) and Roth et al. (19) reviewed the literature to 1994 and concluded that the association is essentially unproved. The epidemiological studies reviewed in these and later analyses are not of even methodologic quality. An important source of variation is the definition and measurement of the amount and timing of alcohol intake. Some of the categories are labeled recent use, recent and past use, current use, lifetime use, usual intake, use in the preceding year, use in the preceding 5 years, use more or less for 4 days per week, use per week, moderate use, infrequent use, use per day, use per month, and use with meals. The control groups of abstainers are variably defined, including using less than 10 grams/week (20), not having used alcohol in the last five years (21), or just "ex-drinkers" (22). Early case-control studies used hospital controls, and more recent ones population controls. Roth et al. (19) demonstrated that studies using hospital controls had considerably higher relative risks than those using community controls. Screening programs are also suspect because controls may be self-selected to volunteer (20). Under-reporting of alcohol consumption is of course common and may bias some studies, particularly when information has been collected by telephone (21). Some studies were begun many years ago and were then reanalyzed when an association between alcohol and breast cancer was suggested. For example, in one study published in 1988, the questionnaires had been collected in 1959 (22).

As previously mentioned, the relative risks reported for breast cancer are very small, particularly with moderate levels of alcohol consumption. In 1994, Longnecker (23) updated his previous review to include 38 studies that passed his methodological criteria for meta-analyses. The relative risk for one drink a day was only 1.1, that for 2 drinks a day 1.2, and that for 3 drinks a day 1.38. The variations in the estimate of relative risk per drink per day reported across studies varied from 0.55 to 2.05. Thus, some studies actually reported a protective effect of alcohol. The most recent and well publicized meta-analysis was that of Smith-Warner et al. in 1998 (24), which reported on 6 cohort studies, each including more than 200 cases of breast cancer. The relative risk up to 30 grams alcohol a day varied from 0.99 to 1.16, and the confidence intervals extended below unity. Thus, no significantly increased risk was demonstrated up to 2 to 3 drinks a day. At levels of 30 to 60 grams alcohol a day, which many consider excessive for women, the relative risk was only 1.4, and inexplicably declined to 1.3 with consumption of more than 60 grams a day. The latter value is probably in the range of alcohol abuse. Although Smith-Warner et al. claim that trend analysis of this meta-analysis

shows a significant trend of risk with increasing consumption, there is actually no evidence for an excess risk at levels generally thought of as moderate. Only one category, namely 30 to 60 grams a day, is itself significant, and the risk up to 30 grams a day clearly shows neither an effect nor a trend. In this respect statistical tests for trends among large numbers of subjects are almost always significantly different from no trend. In spite of the dubious nature of these data, the authors inexplicably concluded that there is a linear and causal association of alcohol consumption with the risk of breast cancer.

The report of Zhang, et al (25) describes the Framingham Study, further supports my view that moderate consumption of alcoholic beverages does not increase the risk of breast cancer. This study followed almost 5,000 women for 24-40 years and reported an actual reduction in breast cancer risk among women who consumed moderate amounts of alcohol. Assigning a relative risk of 1.0 to non-drinkers, relative risks of 0.7 to 0.8 were found in women who drank up to or more than 15 gm of alcohol a day. In his Invited Commentary on this paper (26), Dr. Longnecker apparently recants by stating that "The Framingham results and the results of other studies that do not support a relation of alcohol with breast cancer, raise the possibility of effect modifiers or exposure characteristics that protect against an increased risk of breast cancer in drinkers. **These results remind us that the issue of causality remains unresolved."**

The alleged increase in the relative risk for breast cancer associated with alcohol consumption is very small indeed when compared to most known risk factors for breast cancer, which bestow a relative risk of three or more. Utilizing the Bradford Hill criteria (27), I detect a lack of consistency in the epidemiological studies, weak associations, dubious dose-response gradients (which are usually not monotonic), and variations in temporal relationships. Alcohol abuse, which should be discouraged on other grounds, is beset by such confounding possibilities that a causal relationship with regard to breast cancer remains problematic.

**Alcoholic Beverages and Cancer of the Esophagus**

A number of studies have claimed an association between alcohol consumption and cancer of the esophagus, and indeed IARC listed this tumor as evidence for the carcinogenicity of alcohol. However, confounding by factors other than alcohol is particularly important in the case of this particular tumor, and the studies upon which IARC and the NTP relied are seriously flawed by a lack of appropriate controls. Esophageal cancer is strongly linked to cigarette smoking (28), and attempts to adjust for this habit in the case of esophageal cancer have been highly questionable. As is the case with other cancers allegedly linked to alcohol consumption, a conclusive association between moderate alcohol consumption and esophageal cancer is lacking, and meaningful relative risks are reported only at high levels of alcohol intake, which are probably in the range of alcohol abuse or alcoholism. Many of the studies do not distinguish between squamous carcinoma and adenocarcinoma, the latter showing a substantial increase in recent years. Most or all adenocarcinomas of the esophagus arise in an area of gastric metaplasia termed Barrett's esophagus. This condition reflects gastroesophageal reflux disease, a disorder that is particularly common in alcoholics and in smokers. In this respect, alcohol has been demonstrated to relax the lower esophageal sphincter, thereby permitting the reflux of gastric contents into the lower esophagus. Persons who have experienced heartburn after excessive indulgence in alcoholic beverages will attest to this effect. With respect to squamous carcinoma,

chronic esophagitis and achalasia (which permits acid reflux) have been reported to increase the risk. In addition, esophageal cancer is particularly sensitive to a wide variety of environmental factors, as evidenced by the existence of an esophageal cancer belt that ranges from the Caspian littoral across Asia to Northern China. In areas of this geographic belt, the incidence of esophageal cancer is as high as 100 times that in the United States, despite the fact that many of the populations neither smoke nor drink. In light of these considerations, it is inappropriate at this time to list alcohol per se as a carcinogen for the esophagus.

**Alcoholic Beverages and Oropharyngeal Cancer**

As with the other cancers discussed above, evidence for an increased risk of oropharyngeal cancer in moderate drinkers who do not smoke is slim to none. Even in studies that have tried to control for smoking, the effect of tobacco is statistically adjusted rather than directly observed. In chronic alcohol abusers, the risk of oropharyngeal cancer in non-smokers has been difficult to measure, owing to the small numbers of alcoholics who do not smoke. Even assuming that the increased risk in alcoholics is real, it should be noted that it has been proposed that deficiencies of vitamin C, vitamin A, iron, zinc and copper may be related to oral cancer (29). Thus, the role of tobacco and other confounders remains an important question when considering a putative link between alcohol and oropharyngeal cancer.

In conclusion, there is no experimental evidence that alcoholic beverages are carcinogenic. The epidemiological data for associations between the consumption of alcoholic beverages and cancers of the liver, breast, esophagus and oropharynx are inconsistent, poorly controlled, and seriously subject to confounding by other factors. Under these circumstances, it is inappropriate to label alcoholic beverages as a carcinogen for any of these organs.

Very truly yours,

Emanuel Rubin

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Attachment: References

**References**


1. Taubes U: Epidemiology faces its limits. Science 269:164-169, 1995.

2. Brooks PJ: DNA damage, DNA repair and alcohol toxicity. Alcoholism: Clin. Exp. Res. 21:1073-1082, 1997.

3. Sorenson TIA, Orholm M, Bentsen KD, Hoybye G, Eghoje K, Christoffersen P: Prospective evaluation of alcohol abuse and alcoholic injury in men as predictors or or development of cirrhosis. Lancet 2:241-244, 1984.

4. Nalpas B, Berthelot P, Thiers V, Duhamel G, Courouce AM, Tiollais P, Brechot C: Hepatitis B virus multiplication in the absence of usual serological markers. A study of 146 alcoholics. J. Hepatol. 1:89-97, 1985.

5. Laskus T, Slusarczyk J, Lupa E, Cianciara J: Liver disease among Polish alcoholics. Contribution of chronic active hepatitis to liver pathology. Liver 10:221-228, 1990.

6. Brechot C, Nalpas B, Courouce AM, Duhamel G, Callard P, Carnot F, Tiollais P, Berthelot P: Evidence that hepatitis B virus has a role in liver cell carcinoma in alcoholic liver disease. N. Engl. J. Med. 306:1384-1387, 1982.

7. Saunders JB, Wodak AD, Morgan-Capner P, White YS, Portmann B, Davis M, Williams R: Importance of markers of hepatitis B virus in alcoholic liver disease. Br. Med. J. 286:11851-11854, 1983.

8. Nakanuma Y, Ohta G: Morphology of cirrhosis and occurrence of hepatocellular carcinoma in alcoholics with and without HBsAg and in non-alcoholic HBsAg-positive patients. A comparative autopsy study. Liver 3:231-237, 1983.

9. Lehmann FG, Martini GA: Incidence of primary liver cell carcinoma in liver cirrhosis: 5 year prospective study. Digestion 14: 530-531, 1976.

10. Mendenhall CL, Seeff L, Diehl AM, Ghosn SJ, French SW, Gartside PS, Rouster SD, Buskell-Bales Z, Grossman CJ, Rosselle GA, et al: Antibodies to hepatitis B virus and hepatitis C virus in alcoholic hepatitis and cirrhosis: Their prevalence and clinical relevance. The VA Cooperative Study Group (No. 119). Hepatology 14:581-589, 1991.

11. Nalpas B, Driss F, Pol S, Hamelin B, Housset C, Brechot C, Berthelot P: Association between HCV and HBV infection in hepatocellular carcinoma and alcoholic liver disease. J. Hepatol. 12:70-74, 1991.

12. Bode JC, Biermann J, Koshe KP, Walker S, Bode C: High incidence of antibodies to hepatitis C virus in alcoholic cirrhosis: Fact or fiction? Alcohol Alcohol 26:111-114, 1991.

13. Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, Ventura M, Vall M, Bruguera M, Bru C, et al: Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 2:1004-1006, 1989.

14. Pares A, Barrera JM, Caballeria J, et al: Hepatitis C virus antibodies in chronic alcoholic patients: Association with severity of liver injury. Hepatology 12:1295-1299, 1990.

15. Williams RR, Horm JW: Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. J. Natl. Cancer Inst. 58:525-547, 1977.

16. McPherson K, Cavallo F, Rubin E: Alcohol & Breast Cancer. Health Issues Related to Alcohol Consumption, ILSI Europe, 1999, In Press.

17. Steinberg J, Goodwin PJ: Alcohol and breast cancer risk (review). Breast Cancer Res. Treat 19:221-31, 1991.

18. Shatzkin A, Longnecker MP: Alcohol and breast cancer. Where are we now and where do we go from here? Cancer 74(suppl)(3):1101-1110, 1994.

19. Roth HD, Levy PS, Shi L, Post E: Alcoholic beverages and breast cancer: some observations on published case-control studies. J. Clin. Epidemiol. 47:207-216, 1994.

20. Talamini R, La Vecchia C, Decarli A, et al: Social factors, diet and breast cancer in a northern Italian population. Br. J. Cancer 49:723-729, 1984.

21. Webster LA, Wingo PA, Layde P, et al: Alcohol consumption and risk of breast cancer. Lancet 2:724-726, 1983.

22. Sneyd MJ, Paul CH, Spears GFS, et al: Alcohol consumption and risk of breast cancer. Int. J. Cancer 48:812-815, 1991.

23. Longnecker MP: Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. Cancer Causes and Control 5:73-82, 1994.

24. Smith-Warner SA, Speigelman D., Yuan S, et al: Alcohol and breast cancer in women. A pooled analysis of cohort studies. JAMA 279:535, 1998.

25. Zhang Y, Kreger BE, Dorgan JF, Spainsky GL, Cupples LA, Ellison RC: Alcohol consumption and risk of breast cancer: The Framingham Study Revisited. Am. J. Epidemiol. 149(2):93-98, 1999.

26. Longnecker MP: The Framingham results on alcohol and breast cancer. Am. J. Epidemiol. 149(2):102-104, 1999.

27. Bradford Hill: The Environment and Disease: Association or Causation? Proc. Roy. Soc. Med. 295-299, 1971.

28. Rubin E, Farber JL: Pathology, 3rd Edition, Eds., J.B. Lippincott-Raven, Philadelphia, 1998.

29. Gerson SJ: Oral cancer. Crit. Rev. Oral Biol. Med. 1(3):153-166, 1990.